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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
[redacted]	
ART UNIT	PAPER NUMBER
1644	14

DATE MAILED: [redacted]

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/872,527	Applicant(s) Guo, Y.
	Examiner Thomas Cunningham	Group Art Unit 1644

X Responsive to communication(s) filed on *Nov 23, 1998*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-22 and 33-65* is/are pending in the application.

Of the above, claim(s) *5, 11, 14-19, 39-48, 55, 56, 58-62, 64, and 65* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-4, 6-10, 12, 13, 20-22, 33-38, 49-54, 57, and 63* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 1-22 and 33-65 are active. Claims 1-4, 6-10, 12, 13, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49-54, 57, and 63 read on the elected species and are subject to examination.

2. Applicant previously elected in Paper No. 5 (mailed 2/9/98) the species of bridge molecule: bispecific monoclonal antibodies. Claims 1-22 and 33-48 encompass bispecific monoclonal antibodies. Applicant further elected the method exemplified in Example 6.6 and Figs 5 and 6. This example encompasses use of CD28:gp55 bispecific monoclonal antibodies. Therefore, the elected species is limited to bispecific monoclonal antibodies that bind to both CD28 and the gp55 tumor cell antigen from HEPA 1-6 cells. Further, the elected species of composition and method as defined by Example 6.6. is limited to cytokine-treated (CT) HEPA 1-6 cells that have been pretreated *in vitro* with the combination of TNF-α and IFN-γ and then armed with the CD28:gp55 bispecific monoclonal antibody for the purpose of treating murine hepatoma. Claims 1-4, 6-10, 12, 13, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49-54, 57, and 63 read on the elected species.

Claims 5 (transfection of target diseased cells), 11 (attachment via covalent bond), 14-15 (virally-infected cells), 16-17 (two or more bridge molecules), 18-19 (binding sites for more two or more costimulatory molecules), 39-41 (*in vivo* administration of cytokines), 42-48 (two or more bridge molecules), 55-56 (two or more bridge molecules or binding sites), 58-62 and 64-65 (transfection of target diseased cell) do not read on the elected species and are withdrawn from consideration. Applicant is required to verify and confirm which of claims 1-22 and 33-65 read on the previously elected species.

3. Applicant has confirmed on page 6 of the last response (Paper No.7) that Nature Medicine 4:1-5 (April 1997) does not refer to an article by Guo et al.

4. Claims 1-22 and 33-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. While the elected species of bridge molecule is a constructed bispecific antibody that binds to gp55 and to CD28, it is unclear what the intended scope of the term "bridge molecule" is. Does this term exclude molecules like B7 which may bridge a T cell to an antigen presenting cell by binding CD28 on the T cell and being anchored to an antigen presenting cell via a transmembrane domain? Different prior art issues may eventually emerge if the term "bridge molecule" reads on B7 (or other ligands) that are transfected into a target/tumor cell.

5. Claims 1-22 and 33-65 are rejected under 35 U.S.C. 112, first paragraph as lacking adequate description and enablement for bispecific antibodies comprising a determinant for gp55.

It is apparent that the gp55 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. The deposited antibody must be the antibody used to produce the bispecific antibodies that cure murine hepatoma. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit. If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

6. Claims 1-4, 6-10, 12, 13, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49-54, 57, and 63 are rejected under 35 U.S.C. first paragraph, because the specification, while being enabling for treatment of immunogenic tumors such as HEPA 1-6 hepatomas, does not reasonably provide enablement for treatment of nonimmunogenic tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Chen et al., J. Exp. Med. 179:523-532 (1994) teaches that immunization of animals with nonimmunogenic tumors, even when the tumors were transfected with B7 (an activation ligand for CD28) did not

increase tumor specific CTL activity, see abstract. Further page 530, second column teaches that the presence or absence of MHC Class I molecules is not a reliable predictor of immunogenicity because some nonimmunogenic tumors express high levels of MHC Class I molecules. Tumors may fail to process or present tumor-associated antigens to T cells or be incapable of proper signaling, even in the presence of MHC Class I molecules and thus be nonimmunogenic, see col. 1 on page 530.

7. The prior rejections under 35 U.S.C. 112, first paragraph are withdrawn for the elected species of composition and method exemplified in Example 6.6.

8. Claims 1-4, 6-10, 12, 13, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49-54, 57, and 63 are rejected under 35 U.S C. 103(a) as being unpatentable over Wang et al., Int. J. Cancer 51:962-967 (1992) or Vanky et al., Semin. Cancer Biol. 2(1):55-62 (Feb. 1991) in view Renner et al., Science 264:833 (1994) or Bohlen, Blood 82:1803-1812 (1993), admissions in the specification, Darlington et al., JNCL 64:809 (1980), Chapoval et al., J. Immunol. 155:1296-1303 (1995) and Krummel et al., J. Exp. Med. 182:459-465 (1995).

The claims are directed to compositions comprising and methods of using bispecific monoclonal antibodies (Bi-MAbs) comprising a determinant that binds to CD28 and a determinant that binds to a tumor-associated antigen such as gp55.

Wang et al., page 962, second column teach cytokine-induced elevation of MHC calss-I and ICAM-1 (CD54) expression on tumor cells treated *ex vivo* with TNF-α and IFN-γ. Such

induction is taught to resut in tumor cells that interact more readily with autologous lymphocytes and induce CTLs that even lyse untreated tumor cells. Vanky et al. teach that *in vitro* treatment of tumor cells with TNF-α and IFN-γ induces expression of MHC Class I antigens and ICAM-1 and that expression of class I MHC antigens is necessary for recognition of the tumor cells by autologous lymphocytes that lyse the tumor cells.

Wang et al. and Vanky et al. do not teach bispecific antibodies that bind to CD28 and to a tumor-associated antigen like gp55 or provide motivation for bridging tumor cells to CTL's via CD28.

Renner et al. teach that bispecific monoclonal antibodies to bind to CD28 and to tumor-associated antigens (CD30) in order to "target human T cells to the tumor cells in vivo". The exact identity of the antibody that binds to the target cell (for the elected species gp55) does not appear to be critical to the invention, see e.g. page 10, lines 25-27 of the specification. Assuming *arguendo* that use of antibodies recognizing gp55 from HEPA 1-6 is a critical feature of the invention, page 29 of the specification admits that HEPA 1-6 cells were known in the prior art. Darlington et al. also teach such hepatoma cells. Page 32, lines 10-15 admit that methods of making monoclonal antibodies were known and page 33, lines 4-7 admit that methods of making bispecific antibodies were known.

Bohlen et al. also teach targeting of T cells to tumor cells using bispecific antibodies comprising a ligand for CD28, see abstract and page 1810 indicates that optimal responses may be maintained by the administration of CD28 antibodies to ensure proliferation and stimulation of tumor-specific T cells.

Chapoval et al. teach that bispecific antibodies that bridge T cells and tumor cells trigger activation of T cells and retarget such activated T cells to tumor cells resulting in lysis of tumor cells, see abstract and pages 1301-1302.

Krummel et al. teach that CD28 is the "major costimulatory molecule for proliferation of T cells" and that antibody engagement of CD28 on T cells augments T cell responses and can supply costimulation to T cells encountering APCs deficient in costimulation (Hepa 1-6 cells are deficient in antigen presentation because they lack MHC Class I expression, see pages 29-30 of the specification).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to treat tumor cells with IFN-γ and TNF-α as taught by Wang et al. or Vanky et al. for the purpose increasing the immunogenicity of the tumor cells by inducing expression of molecules like Class I MHC and ICAM-1, and then to arm such tumor cells with bispecific antibodies that bridge the tumor cells to cytotoxic lymphocytes (CTLs) using bispecific antibodies such as those of Renner et al. for the purpose of targeting CTL's to the cytokine-treated tumor cells and costimulating CTLs via binding of the bispecific antibody to the CD28 receptor on CTLs. Based on the teachings of the secondary references one with ordinary skill in the art would have expected that such bispecific antibodies when bound to the cytokine-treated tumor cells of Wang et al. or Vanky et al. would provide costimulation to CTLs via the free CD28 binding ligand and thus enhance the CTL activity. One with ordinary skill in the art would have recognized that cytokine-treated tumor cells would be expected to be more immunogenic based on the teachings of the primary references that bispecific antibodies to tumor cells and to receptors like CD28 on T

cells would target and bridge tumor cells and T cells together and that use of a bispecific antibody comprising a CD28-binding determinant would not only enhance binding/bridging of CTLs to the cytokine treated tumor cells but also provide costimulation of the CTLs via CD28 that would ensure the proliferation and stimulation of tumor-specific T cells.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D., J.D., whose telephone number is (703) 308-3968. Dr. Cunningham can generally be reached Monday through Thursday from 7:30AM to 6:00 PM. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

PRIMARY EXAMINER
GROUP 1800